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The NICE classification for "Ultra-radical (extensive) surgery for advanced ovarian cancer" guidance does not meaningfully predict post-operative complications: a cohort study.

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Running title: Does "Does the term "Ultra-radical" predict morbidity in AOC?

ABSTRACT

Objective: To determine which descriptors of cytoreductive surgical extent in advanced ovarian cancer(AOC) best predict post-operative morbidity.

Design: Retrospective notes review.

Setting: A gynaecological cancer centre in the United Kingdom.

Population: 608 women operated on for AOC in 114 months at a tertiary cancer centre between 16/8/07-16/2/17.

Methods: Outcome data were analysed by six approaches to classify extent of surgery. Standard/ultra-radical surgery; standard/radical/supra-radical surgery; presence/absence of gastrointestinal resections; low/intermediate/high surgical complexity score(SCS); presence of bowel anastomoses and/or diaphragmatic surgery; and presence/absence of multiple bowel resections.

Main Outcome Measures: Major (grade 3-5) post-operative morbidity and mortality

Results: 43(7.1%) patients experienced major complications. Grade 5 complications occurred in 6 patients(1.0%). Patients who underwent multiple bowel resections had a relative risk(RR) of 7.73(95%CI 3.92-15.26), high SCS RR of 6.12(95%CI 3.25-11.52);

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diaphragmatic surgery and gastrointestinal anastomosis RR 5.57(95%CI 2.65 – 11.72); “any gastrointestinal resection” RR 4.69(95%CI 2.66-8.24); ultra-radical surgery RR 4.65(95%CI 2.26-8.79); supra-radical surgery RR 4.20(95%CI 2.35-7.51) of grade 3-5 morbidity as compared to those undergoing standard surgery as defined by NICE. No significant difference was seen in the rate of major morbidity between standard (6/59,10.2%) and ultra-radical (9/81,11.1%) surgery within the cohort who had intermediate complex surgery ($p>0.05$).

Conclusions: Numbers of procedures performed significantly correlates with major morbidity. The number of procedures performed better predicted major post-operative morbidity than the performance of certain “high risk” procedures. We recommend the SCS to define a higher-risk operation. NICE should re-evaluate the use of the term “ultra-radical” surgery.

Funding: None

Keywords: Ovarian cancer; surgery; morbidity; ultra-radical, NICE

Tweetable abstract

Multiple bowel resection is the best predictor of morbidity and more predictive than ‘ultra-radical surgery’

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INTRODUCTION

The management of advanced ovarian cancer (AOC) consists of cytoreductive surgery in conjunction with platinum-based chemotherapy. Traditionally cytoreductive surgery has focused on pelvic, nodal and omental surgery yet increasingly procedures to treat abdomen wide locations of disease have been utilised such as diaphragmatic, splenic, liver and gastrointestinal resections. In spite of studies comparing European and American patients, who received more extensive surgery than UK patients with correspondingly elevated cytoreduction rates (1, 2), it was only in 2013 that the National Institute for Health and Care Excellence (NICE) implemented guidelines for the widespread use of such procedures (3), an approach which was further endorsed by the Chief Medical Officer in their annual report the following year (4).

In their 2013 guidance (3), NICE expressed caution regarding advanced cytoreductive procedures, so called “ultra-radical” surgery, due to the elevated major morbidity rates of 12-19% seen in patients receiving such surgery compared to 4-5% in those receiving “standard” treatment. The NICE guidance was, therefore, defining a group with a perceived elevated risk of morbidity, by the types of procedures performed, not the number of procedures performed. This approach contrasts with previous attempts to describe the extent of surgery, such as that suggested by Alletti (5), where the extent of surgical complexity is determined by the total number of surgical procedures performed rather than the intrinsic perceived risk of individual procedures themselves.

Predicting which patients will have a non-standard recovery following cytoreductive surgery for advanced ovarian cancer remains elusive. Tools such as P-POSSUM (6) or the American College of Surgeons National Surgical Quality Improvement Programme (NSQIP) (7) have limited value in accurately predicting the risk of major complications following multi-visceral resection in ovarian cancer patients (8). A method of predicting postoperative morbidity ideally prior to, but equally at the end of, surgery would be useful for the patient, the surgical team and those planning resource allocation. Such data would also enable national and international comparison.

The aim of this study was to compare the efficacy of various classifications used to describe cytoreductive surgery on their ability to predict the development of post-operative morbidity. In doing so we sought to determine if morbidity in cytoreductive surgery could be explained

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by the cumulative trauma from the number of procedures performed rather than an intrinsic risk profile of certain "ultra-radical" procedures themselves.

METHODS

Patients

We undertook a retrospective review of all patients diagnosed with stage 3 or 4 AOC between 16th August 2007 and 16th February 2017. All patients were managed by subspecialty trained gynaecological oncologists at the Pan-Birmingham Gynaecological Cancer Centre (PBGCC). Cases were identified from the prospectively recorded gynaecological oncology multidisciplinary team (MDT) database after approval was obtained from the hospital research and development department.

Patients were included in this study if they were referred from a local primary care provider to the PBGCC, underwent a midline laparotomy and had a final histological diagnosis of stage 3 or 4 epithelial ovarian, tubal or peritoneal cancer (AOC). Quaternary referrals from outside the region were excluded from this analysis. All patients were considered on an "intention to treat basis" to allow for complete denominator data to be available.

At PBGCC, the initial assessment of women with suspected AOC consists of clinical examination, transvaginal ultrasound scan, serum CA125 assay and CT scan of the thorax, abdomen and pelvis. All imaging is reviewed by specialist gynaecological cancer radiologists. Following discussion at the MDT meeting, women either undergo: primary debulking surgery (PDS) or receive 3-4 cycles carboplatin AUC 6 +/- paclitaxel 175mg/m2 based neoadjuvant chemotherapy (NACT) with an intention to consider interval debulking surgery (IDS), or palliation.

Typically, surgical procedures include pelvic clearance, omentectomy, and lymphadenectomy. More extensive surgery was introduced in 2008. In appropriately selected patients, gastro-intestinal surgery or radical upper abdominal procedures are also undertaken if required. Extensive stripping of the para-aortic lymph nodes is not performed routinely but enlarged para-aortic lymph nodes are resected. Following surgery all histology receives central review by specialist histopathologists.

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Post-operative morbidity is recorded at our institution using the Memorial Sloane-Kettering Cancer Centre complication grading system (9, 10) (Table S1). For this study, only major morbidity (grades 3, 4, and 5) was recorded with patients classified by the highest recorded complication. Morbidity was both retrospectively obtained from patients' notes and prospectively recorded following critical incident review of major morbidity during the weekly MDT discussion.

The following data was recorded: age; BMI; organ of origin; histological subtype; grade; stage; approach to cytoredution (primary or interval debulking surgery); cytoreductive outcome (complete (R0), optimal <1cm (R1) and suboptimal (R2)); SCS; major morbidity (grade 3+).

Data Analysis

Two types of classification systems were evaluated: (i) scoring systems that assessed the types of surgery used to indicate more complex surgery and (ii) scoring systems that measured the numbers of procedures performed. Within this framework six methods of classification were examined (Table 1).

The first approach identifies high-risk surgery by inclusion of certain procedures. Three styles of assessment were evaluated: (i) NICE classification of standard and ultra-radical surgery; (ii) Pomel classification into standard, radical and supra-radical surgery (11); and (iii), a novel assessment grouping patient by the presence or absence of gastrointestinal resections.

For the purpose of this study, gastro-intestinal surgery contributions to cytoreduction was considered ultra-radical if it fulfilled the criteria stated by NICE i.e. multiple resections of the bowel (excluding localised colonic resection) (3). Patients that underwent gastrointestinal surgery that did not meet this definition were analysed in the standard surgery group. Localised colonic resection was taken to mean a rectosigmoid resection.

The second approach examined the number of procedures performed, thereby defining higher risk surgery in terms of the cumulative surgical "load". Three styles of classifications were evaluated : (a) a modified surgical complexity score (SCS), as advocated by Alletti (5), which categorised surgeries into low, intermediate and high complexity groups (Appendix S1); (b) by the presence of bowel anastomoses and/or diaphragmatic surgery; and (c) the presence or absence of multiple bowel resections.

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The SCS was modified to include procedures outside of the SCS with groin dissection, nephrectomy and partial gastrectomy each giving an additional one point to the total score. With respect to diaphragmatic stripping and lymphadenectomy, points were registered only in the context of a systematic regional treatment. (Appendix S1)

We calculated the relative risk of major morbidity detected by the respective criteria with reference to standard surgery as defined by NICE for each of these six descriptions (i, ii and iii and a, b and c) of surgical radicality.

No core outcome sets were relevant for this study. Furthermore, no patient involvement was required, although the results are now used in guidance for women considering cytoreductive surgery for AOC. No funding was received for this study.

Statistical Analysis

Categorical variables were compared with the chi-squared test and parametric and non-parametric continuous variables were compared with the ANOVA or Kruskal-Wallis test respectively. Survival data was calculated using the Kaplan-Meier method. All tests were two-sided and a p-value of less than 0.05 was regarded as being statistically significant.

RESULTS

Between 16th August 2007 and 16th February 2017, 858 patients received treatment for AOC at the PBGCC. Of these, 610 (71%) underwent cytoreductive surgery with 248 (29%) receiving chemotherapy or palliation alone. Of the patients who underwent cytoreductive surgery, 209 (34%) underwent primary debulking surgery (PDS) with 399 (66%) undergoing interval debulking surgery (IDS). R0, R1 and R2 cytoreduction was achieved in 65%, 14% and 21% respectively. Two patients were excluded from the analysis due to inadequate morbidity data. Survival outcomes and other outcomes have been previously published (12-15). 608 patients were therefore available for analysis.

1. Analysis based on NICE classification

When classified by the NICE guidance, 453 (74.5%) patients underwent standard surgery and 155 (25.5%) patients underwent ultra-radical surgery. Overall patient demographics are demonstrated in Table 2. Patients' age, body mass index and grade distribution was similar in both groups. IDS was performed no more frequently (69.9% versus 64.2%, $p > 0.05$) but

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complete cytoreduction rates were significantly higher (87.7% versus 56.7%, $p < 0.0001$) in the ultra-radical group compared to the standard surgery group (Table 2).

Six patients (1%) died (grade 5 morbidity) as a consequence of: bowel ischaemia following mesenteric thrombosis; pneumonia and acute respiratory distress syndrome (ARDS); pancreatitis leading to ARDS; pulmonary embolus; renal failure; and multi-organ failure due to intra-abdominal sepsis. Four of these patients received standard surgery and two ultra-radical surgery with corresponding mortality rates of 0.9% and 1.2% respectively. It should however be noted that of the patients who underwent standard surgery, three of the four deaths occurred in sub-optimally cytoreduced patients. Major morbidity was most commonly due to: post-operative chest drain insertion (n=5); re-operation for bleeding/haematoma (n=5); anastomotic leaks (n=4); or pelvic collections (n=4) (Table 3).

2. Analysis based on Surgical Complexity Score

When classified using the SCS, 400 patients underwent low complexity surgery, 140 patients underwent intermediate complexity surgery and 68 patients underwent high complexity surgery. As the SCS increased, so too did the rate of grade 3+ post-operative complications ($r=0.9$). A similar trend was seen when analysing patients grouped by their SCS score with low, intermediate and high surgical complexity groups experiencing 3.0%, 10.7% and 23.5% major morbidity respectively (Figure S1).

A subgroup analysis was performed examining the difference in major morbidity across the three SCS groups according to PDS or IDS. Major morbidity occurred in 7/136 (5.1%), 4/51 (7.8%) and 5/22 (22.7%) of patients undergoing low, intermediate or high complexity surgery with PDS. In those receiving IDS the corresponding rates of major morbidity were: 5/264 (1.9%), 11/87 (12.6%) and 11/41 (26.8%). No significant difference was seen between PDS and IDS ($p>0.05$).

3. Analysis of relative risks with respect to different methods of classification.

Six approaches (Table 1) were evaluated on their ability to be predictive of complications relative to standard surgery as defined by NICE (Table 4).

The highest relative risks of major complications were seen in definitions assessing the number of procedures performed. Patients who underwent multiple bowel resections were nearly 8 times more likely to have major post-operative morbidity than patients who had

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standard surgery according to the NICE classification (RR 7.73, 95% CI 3.92-15.26). Patients were approximately 6 times more likely to have a major complication relative to standard surgery as defined by NICE if they had a high SCS (RR 6.12 95% CI 3.25-11.52) or received both diaphragmatic surgery with a gastrointestinal anastomosis (RR 5.57 95%CI 2.65 – 11.72).

Definitions based upon the performance of specific procedures were less useful in identifying post-operative morbidity. Patients receiving ultra-radical surgery compared to standard surgery as defined by NICE were only four times more likely to experience major complications (RR 4.65, 95% CI 2.26-8.79). This relative risk was similar to supra-radical surgery as defined by Pomel (RR 4.20, 95% CI 2.35-7.51). However, such definitions were marginally inferior to that of the solitary criteria of "any gastrointestinal resection" (RR 4.69, 95%CI 2.66-8.24). Additionally, patients undergoing ultra-radical surgery as defined by NICE experienced 58.1% of all major complications in the cohort whereas the definition of "any gastrointestinal resection" identified 72.1% of all major complications (Table 4).

To further investigate the potential for the ultra-radical definition to underestimate major morbidity, a comparison was performed amongst all patients with a SCS of 4-7 (intermediate surgical complexity) with patients subdivided into those that received standard surgery and those that received ultra-radical surgery according to NICE. Patients undergoing surgery of intermediate complexity were used in this analysis because within this group there were 59 (42.1%) patients undergoing NICE standard surgery and 81 (57.9%) patients undergoing NICE ultra-radical surgery. Patients undergoing surgery of low complexity predominantly had NICE standard surgery and patients undergoing surgery of high complexity predominantly had NICE ultra-radical surgery, hence both these groups would have provided a meaningless comparison. No significant differences were seen in the rate of major morbidity between standard (6/59, 10.2%) and ultra-radical (9/81, 11.1%) procedures within the cohort who had intermediate SCS scores ($p>0.05$).

4. **Survival data**

The median overall survival (OS) for all patients receiving surgery was 48.2 months (95%CI 40.6-55.8). In patients that underwent PDS and achieved R0, the median OS had not been reached as of August 2017. The estimated mean OS however was 83.9 months (95% CI 75.2 – 92.7). In patients that underwent PDS and achieved R1 or R2, the median OS was 56.3 months (95% CI 25.8-86.8) and 15.0 months (95% CI9.1-20.8) respectively. In patients

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undergoing IDS, the median OS was 57.9 months (95% CI 43.2-72.7) in R0, 33.4 months (95% CI 25.0-41.7) in R1 and 28.4 months (95% CI 21.6 – 35.2) in R2. In patients not receiving surgery, the median OS was 11.7 months (95% CI 8.3 – 15.0).

DISCUSSION

Main findings

Our study demonstrates that the number of procedures performed significantly correlates with an increased risk of major morbidity. Additionally, we found that the number of procedures performed are a better predictor of major post-operative morbidity than the performance of certain "high risk" procedures alone. The NICE definition of ultra-radical surgery was a less useful predictor of major complications compared to the solitary criterion of 'any gastrointestinal resection'.

Strengths and Limitations

The main strength of this study is the availability of total patient descriptors and the volume of cases arising from an early adopter of maximum effort cytoreduction in the UK. As a retrospective review of practice, our results do however need to be interpreted with caution. Certain procedures, including liver resections and partial gastrectomies, were infrequently performed and therefore our results may be inaccurate in patients undergoing these procedures. Furthermore, given the high rate of IDS observed in this study, our findings may be less generalizable to centres performing a greater proportion of PDS. We appreciate the wide confidence intervals and recommend a suitably powered, prospective study to confirm our findings.

Interpretation

As the extent of surgery increases, so too does the risk of major morbidity. It is hardly surprising that patients treated with 'ultra-radical' surgery experience higher rates of major complications than patients managed with standard surgery (16-18). Although surgical complexity has long been associated with post-operative morbidity (19-21), our study is the first to demonstrate that standard and 'ultra-radical' surgery of similar surgical complexities have similar major complication rates suggesting that the actual number of procedures performed is a more important driver of post-operative morbidity than procedure types themselves.

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Of the five studies originally describing their morbidity following the introduction of advanced surgical procedures, all can be considered studies of an ethos change towards multi-visceral resection, and thus it is unsurprising that all demonstrated a mean number of advanced procedures per patient between 1.6 and 2.2 (2, 16-18, 22). Similar results were seen in single centre studies examining isolated organ resection in cytoreductive surgery. Magtigbays' study of 112 patients undergoing splenectomy witnessed 61 additional urological/colorectal procedures (23). Tsoloakidids' study of 89 patients undergoing diaphragmatic resection saw 32 additional advanced procedures utilised (24). Isolated pelvic disease is uncommon in AOC (25) and hence multiple advanced procedures may be required to achieve cytoreductive targets.

Our findings indicate that the morbidity risk is higher after high complexity surgery, diaphragmatic surgery with a colorectal anastomosis and multiple bowel resections. This supports the theory that the overall surgical 'load' is a significant driver of post-operative morbidity and is better predictor than certain specific procedures.

'Ultra-radical' procedures have been utilized in isolation in other conditions with acceptable safety profiles (26-28) and previous reviews of advanced surgical procedures at the PBGCC only observed significantly increased morbidity in those patients who underwent multi-visceral resections (12, 29).

In Alleti's paper, although surgical complexity was associated with major morbidity, subgroup analysis did not demonstrate a difference between various age and morbidity groups at similar surgical complexity levels (20). Similar findings were seen when the age-adjusted Charleston co-morbidity index was used in primary (10) and interval (14) cytoreductive surgeries. Such surprising results may be due to insufficient power as all studies showed a non-significant increase in post-operative morbidity with increasing age and morbidity. Therefore, a meta-analysis would be strongly recommended. It is likely that other factors manipulate the baseline risk such as: serum albumin; performance status; age; and preoperative morbidities. In our study, despite the high operated patient rate, risk from intervention may be underestimated in the elderly or co-morbid. It is essential that large core outcome data sets are developed with pooling of data to better describe individual patients' risks of post-operative morbidity. Such data would give an additional way of benchmarking centre performance in addition to general cohort descriptors (13) and survival data.

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Attempts to describe the postoperative course for individual patients have proven difficult in the gynaecological oncological setting. Pre-operative predictors of morbidity such as P-POSSUM (6) or the American College of Surgeons National Surgical Quality Improvement Programme (NSQIP) (7) both have limited value in accurately predicting the risk of major complications following multi-visceral resection in ovarian cancer patients (8). Although international guidance incorporates complications rates into the therapeutic pathways, predicting postoperative morbidity in cytoreductive surgery for individual patients remains elusive (30).

The SCS is a marker of surgical 'load' both as a measure of numbers of procedures as well as a weighting of each of the constituent parts. Although we have modified the SCS to include groin lymphadenectomy, nephrectomy and gastrectomy, our weighting was arbitrarily set at 1. There are also procedures worthy of inclusion such as resection around the porta hepatis, the lesser sac, and coeliac axis and further studies to define what weight the SCS should give to these procedures should be encouraged. Despite this limitation, our study shows postoperative morbidity positively correlating with Aletti's SCS. Additionally, it demonstrates that the relative risk of major morbidity is higher with definitions that assess *numbers* of procedures rather that those that assess *types* of procedures. We suggest that assessing surgery load is more useful than looking at what surgery is to be performed. It could be argued that the numbers of procedures needed cannot be predicted pre-operatively but studies pertaining to pre-operative prediction of required surgery have often focused on resectibility rather than surgical complexity (31). We suggest that, if it is considered appropriate to proceed with surgery, a crude assessment of the surgical complexity required can be achieved using clinical examination, cross-sectional imaging and, in selective cases, diagnostic laparoscopy. This assessment would allow for more informed patient choice regarding whether to undergo surgery.

In its next review of the guidance regarding ultra-radical surgery, we urge NICE to clarify the role of gastrointestinal surgery in both standard and ultra-radical settings. In its present state, NICE defines 'standard' surgery as 'radical' with constituent parts of 'bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and lymphadenectomy'(3) with no mention of bowel surgery. Ultra-radical surgery however requires 'multiple resections of the bowel (excluding localised colonic resection)'(3). There therefore remains a grey area

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between standard and ultra-radical surgery encompassing single gastrointestinal resections especially of the small bowel and the extent of resection that renders a colonic resection ‘localised’.

In our study, the NICE definition of ultra-radicality failed to predict morbidity when compared to ‘any gastro-intestinal resection’. We therefore need to use a more accurate classification of surgical radicality to better inform patients, surgeons and resource allocators in the management of AOC.

CONCLUSION

Defining cytoreductive surgery in AOC in a meaningful way remains elusive. Traditional terms such as standard, radical, supra-radical or ultra-radical reflect on the progression of gynaecological oncology surgery from limited pelvic surgery to abdomen-wide surgery that covers the disease distributions. Such terms are emotive, often poorly defined and do little to quantify risks for patients. The numbers of procedures performed appears to be a more significant predictor of morbidity. We suggest using the approach advocated by Aletti to define a higher-risk operation and suggest that it should be the basis of any future development by NICE regarding the acceptable extent of surgery

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None

DISCLOSURE OF INTERESTS

Sean Kehoe has received fees for lecturing for Astra Zeneca and Roche.

Janos Balega has received personal fees from Astra Zeneca and Roche.

All other authors have no declarations. Completed disclosure of interest forms are available to view online as supporting information.

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CONTRIBUTION OF AUTHORSHIP

Study Concept: AP, KS, JB, SS, AE

Data collection: AP, RP, AE

Manuscript preparation: AP, SS, JB, SK, RP, JN, KS, AE

ETHICS APPROVAL

This study had been approved by the hospitals' research and development department. According to the Medical Research Council Health Research Authority, ethical approval was not required for this study.

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None

TABLE/FIGURE CAPTION LIST

ONLINE SUPPORTING MATERIAL

Table S1: Memorial Sloane–Kettering Cancer Centre complication grading system.

Figure S1: Major postoperative morbidity in patients undergoing low, intermediate and high complexity surgery.

Appendix S1: Adjusted Aletti surgical complexity score (SCS)

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Table1: Six descriptions of surgical radicality.

	Classification	Groups	Criteria
TYPES OF PROCEDURES	NICE	Standard	Total abdominal hysterectomy, Bilateral salpingo-oophorectomy, Omentectomy, Pelvic and/or para-aortic lymphadenectomy, Bowel surgery outside the definition of "ultraradical" (localised colonic resection, non-multiple bowel resection)
		Ultra-radical	Diaphragmatic stripping, Extensive peritoneal stripping, multiple resections of the bowel (excluding localised colonic resection), Liver resection, Partial gastrectomy, Cholecystectomy, Splenectomy
	Pomel	Standard	Hysterectomy, Bilateral salpingo-oophorectomy, Pelvic peritonectomy, Total omentectomy, Appendicectomy, Pelvic and/or para-aortic lymphadenectomy
		Radical	Recto-sigmoid resection
		Supra-radical	Diaphragmatic stripping, Liver resection, Cholecystectomy, Splenectomy, Any digestive resection excluding recto-sigmoid resection
	Any Gastrointestinal resection	No Gastro intestinal resection	No Gastro intestinal resection
		Any Gastrointestinal resection	Any Gastrointestinal resection
NUMBERS OF PROCEDURES	Aletti's Surgical Complexity Score	Low Complexity	SCS 0-3
		Intermediate Complexity	SCS 4-7
		High Complexity	SCS ≥8
	Multiple bowel resections	≤ One bowel resection	≤ One bowel resection
		Two or more bowel resections	Two or more bowel resections
	Diaphragmatic Surgery with colo-rectal anastomosis	No diaphragmatic surgery or colorectal anastomosis	No diaphragmatic surgery or colorectal anastomosis
		Diaphragmatic surgery without colorectal anastomosis	Diaphragmatic surgery without colorectal anastomosis
		Colorectal anastomosis without diaphragmatic surgery	Colo-rectal anastomosis without diaphragmatic surgery
		Diaphragmatic surgery and colorectal anastomosis	Diaphragmatic surgery and colorectal anastomosis

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Table 2: Overall cohort data as defined by NICE.

	NICE: Standard n = 453 n (%)	NICE: Ultraradical n=155 n (%)	*p*	Total Cohort n= 608 n (%)
Age	65.1 IQR 57.0-73.1	63.0 IQR 55.0-71.6	>0.05	64.5 IQR 56.7-72.7
BMI	26 IQR 22-29	26 IQR 22-29	>0.05	26 IQR 22-29
Site				
Ovary	318 (70.1)	90 (58.1)	0.006	408 (67.1)
Fallopian Tube	80 (17.7)	44 (28.4)	0.004	124 (20.4)
Primary Peritoneal	55 (12.4)	21 (12.7)	>0.05	76 (12.5)
Histology				
Serous	382 (84.3)	143 (92.3)	0.01	524 (86.2)
MMMT	22 (4.9)	6 (3.9)	>0.05	28 (4.6)
Clear cell	16 (3.6)	4 (2.4)	>0.05	20 (3.3)
Mixed	14 (3.2)	2 (1.2)	>0.05	16 (2.6)
Anaplastic/Undiffererentiated	4 (0.9)	0 (0.0)	>0.05	4 (0.7)
Endometroid	8 (1.8)	0 (0.0)	>0.05	8 (1.3)
mucinious	3 (0.7)	0 (0.0)	>0.05	3 (0.5)
Unknown	4 (0.9)	0 (0.0)	>0.05	4 (0.7)
Grade				
1	23 (5.2)	7 (4.2)	>0.05	30 (4.9)
2	5 (1.1)	2 (1.2)	>0.05	7 (1.2)
3	413 (91.1)	145 (93.5)		558 (91.8)
Unknown	12 (2.7)	0 (0.0)	>0.05	12 (2.0)
Stage				
3	345 (76.2)	110 (71.0)	>0.05	455 (74.8)
4	108 (23.8)	45 (29.0)	>0.05	153 (25.2)
Approach				
IDS	291 (64.2)	108 (69.7)	>0.05	399 (65.6)
PDS	162 (35.8)	47 (30.3)	>0.05	209 (34.4)
Cytoreduction				
R0	256 (56.5)	137 (88.4)	< 0.0001	393 (64.6)
R1	76 (16.8)	10 (6.5)	0.001	86 (14.1)
R2	121 (26.7)	8 (5.2)	< 0.0001	129 (21.2)

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Table 3: Major complications in Standard and Ultra-radical surgery as defined by NICE.

	Major Complications	NICE Standard	NICE Ultra-radical	Total Cohort
Grade 3	Chest drain insertion (+/-) Bronchoscopy	1	4	5
	Return to theatre (Haematoma/Bleeding)	2	2	4
	Return to theatre (Collection)	2	2	4
	Image guided drainage (collection)	0	3	3
	Return to theatre (No pathology found)	2	1	3
	Return to theatre (Revision of stoma)	2	0	2
	OGD (Bleeding)	1	0	1
	Return to theatre (Closure of laparostomy) and OGD (Bleeding)	0	1	1
	Return to theatre (Removal of Packs)	1	0	1
	Return to theatre (Wound dehiscence)	1	0	1
	Grade 3 Total	12	13	25
Grade 4	Return to theatre (Anastomotic leak)	2	2	4
	Return to theatre (Splenectomy, liver failure, renal failure, pancreatitis	0	1	1
	Cardiac pacing after Sinus arrest	0	1	1
	Intraoperative splenectomy for iatrogenic bleeding	0	1	1
	Return to theatre (Anastomotic leak) + Sheath dehiscence	0	1	1
	Return to theatre (Gastric perforation) Subsequent Enterocutaneous fistula and tracheostomy	0	1	1
	Return to theatre Spinal surgery for paraspinal infection	0	1	1
	Renal failure	0	1	1
	Urinary Tract Fistula	0	1	1
	Grade 4 Total	2	10	12
Grade 5	Renal Failure	1	0	1
	Bowel ischaemia secondary to mesenteric thrombosis	1	0	1
	Intra-abdominal sepsis	1	0	1
	Pulmonary Embolus	0	1	1
	Pancreatitis and ARDS	0	1	1
	Pneumonia, ARDS and Renal failure	1	0	1
	Grade 5 Total	4	2	6

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Table 4: Postoperative morbidity by different radicality definitions.

	Prediction model	Number of patients	Major complications n (%)	% complications detected	RR Overall	95% CI
NICE	Standard surgery	453	18 (4.1)	41.9%	1.00	
	Ultra-radical surgery	155	25 (15.1)	58.1%	4.65	2.26-8.79
POMEL	Standard surgery	380	8 (2.1)	18.6%	0.55	0.24-1.25
	Radical surgery	61	8 (13.1)	18.6%	3.41	1.54-7.56
	Supra radical surgery	167	27 (16.2)	62.8%	4.20	2.35-7.51
GASTROINTESTINAL TRACT	No Gastrointestinal Surgery	436	12 (2.8)	27.9%	0.72	0.35-1.48
	Gastrointestinal Surgery	172	31 (18.0)	72.1%	4.69	2.66-8.24
MULTIPLE BOWEL RESECTIONS	One or less bowel resections	571	32 (5.6)	74.4%	1.46	0.82-2.59
	Two or more bowel resections	37	11 (29.7)	25.6%	7.73	3.92-15.26
DIAPHRAGMATIC SURGERY AND COLORECTAL ANASTOMOSIS	No diaphragmatic stripping or gastrointestinal anastomosis	452	16 (3.5)	37.2%	0.92	0.47-1.80
	Diaphragmatic stripping/resection	43	5 (11.6)	11.6%	3.02	1.17-7.79
	Gastrointestinal Anastomosis	71	13 (18.3)	30.2%	4.76	2.42-9.37
	Diaphragmatic stripping and gastrointestinal anastomosis	42	9 (21.4)	20.9%	5.57	2.65-11.72
ALETTI	Low surgical complexity	400	12 (3.0)	27.9%	0.78	0.38-1.61
	Intermediate surgical complexity	140	15 (10.7)	34.9%	2.79	1.43-5.43
	High Surgical complexity	68	16 (23.5)	37.2%	6.12	3.25-11.52

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